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(54) Process for selectively producing hydrate crystals

Verfahren zur selektiven Herstellung von Hydratkristallen

Procédé pour la préparation sélective de cristaux d'hydrate

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(56) References cited:
EP-A- 0 206 283
DD-A- 203 719

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Description

FIELD OF THE INVENTION

This invention relates to a process for the selective production of the antimicrobial compounds (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate and monohydrate.

BACKGROUND OF THE INVENTION

Levofloxacine, which is a common name of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate in accordance with JAN (Japanese Accepted Name), is a compound demonstrating a high antimicrobial effect and high safety (refer to JP-A-62-252790 or EP-A-0 206 283). The terms "JP-A" and "EP-A" as used herein mean an "unexamined published Japanese patent application" and "European patent publication", respectively. Thus, it is expected as an excellent synthetic antimicrobial agent.

In addition to levofloxacine which is a hemihydrate, crystals of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid may be present in the form of a monohydrate differing in the number of water molecules in the crystal, or as anhydrous crystals obtained by dehydrating these hemi- and monohydrates.

A process is known for the production of levofloxacine which involves recrystallization or crystallization of levofloxacine from a solvent mixture of ethanol and diethyl ether or concentrated aqueous ammonia and ethanol (refer to JP-A-62-252790 or EP-A-0 206 283 as cited above). However, the use of the latter solvent mixture may cause the crystallization of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid monohydrate, which will simply be called "monohydrate" hereinafter, together with the target levofloxacine (the hemihydrate form). The conversion of this monohydrate into the hemihydrate may be difficult to achieve in practice. Namely, when crystal water is removed from the monohydrate and the anhydrous crystals thus obtained are allowed to take up moisture, only the original monohydrate is obtained. When levofloxacine is contaminated with the monohydrate, therefore, the recrystallization or crystallization must be conducted till such contamination disappears.

Furthermore, anhydrous crystals obtained by removing crystal water cause blocking or sticking, and the industrial operations with them become troublesome. Accordingly, a method of preparing hydrated crystals by hydration of the dehydrated crystals is unsuitable as an industrial process.

DD-A-203 719 discloses the recrystallization of the corresponding racemic compound from various solvents. In case dimethyl formamide or a mixture of chloroform and methanol or a mixture of concentrated ammonia and methanol or ethanol is used, the anhydrous form is obtained whereas the 3/2 hydrate is obtained in case a mixture of chloroform, methanol and water is used as recrystallisation solvent.

SUMMARY OF THE INVENTION

Under these circumstances, the present inventors have conducted extensive studies. As a result, they have discovered that (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate, i.e., levofloxacine, free from any monohydrate can be obtained by controlling the crystallization conditions. In addition, the inventors discovered that the solvent can be entirely removed without converting the product into the anhydrous crystals with undesirable properties such as sticking or blocking, and the target hemihydrate can be obtained by controlling the drying conditions. Thus, they have confirmed that the hemihydrate or monohydrate can be easily obtained without being contaminated with one another.

The above and other objects and advantages are obtained by a process for selectively producing (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3,-de][1,4]benzoxazine-6-carboxylic acid hemihydrate which comprises

(i) stirring a slurry of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperainyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4] benzoxazine-6-carboxylic acid monohydrate or a mixture of the monohydrate and the hemihydrate thereof in an aqueous water miscible solvent containg water in an amount of 10 % by volume or less, at a temperature and for a period of time appropriate to substantially avoid monohydrate formation,

(ii) dissolving said monohydrate or a mixture of said monohydrate and said hemihydrate in an aqueous water miscible solvent which is selected from methanol, ethanol, propanol and acetone and which contains 2 to 10 % water by volume, under conditions which substantially avoid monohydrate formation, the solvent being used in an

amount, by volume, of 4 to 8 times the amount, on a weight basis, of said monohydrate or said mixture, and crystallizing the hemihydrate from said solvent by cooling or

(iii) dissolving anhydrous (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid in an aqueous solvent which is selected from methanol, ethanol, propanol and acetone and which contains 2 to 10 % water by volume, under conditions which substantially avoid monohydrate formation, the solvent being used in an amount, by volume, of 4 to 8 times the amount, on a weight basis, of said anhydrous carboxylic acid, and crystallizing the hemihydrate from said solvent by cooling.

The invention also relates to a process for selectively producing (S)-9-fluoro-3-methyl-10-1(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-7-carboxylic acid monohydrate which comprises stirring a slurry of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate or a mixture of the hemihydrate and the monohydrate thereof in water or an aqueous solvent containing more than 10 % water at a temperature and for a period of time apropriate to substantially avoid monohydrate formation.

Detailed description of the invention:

In the process for producing the hemihydrate

The solvent has a water content which substantially prevents monohydrate crystal formation. One solvent which is preferably used is aqueous ethanol. More preferably, the solvent is aqueous ethanol with a water content ranging from about 2 to about 10%, more preferably from 4 to 5% (v/v). All water contents used herein are by volume per volume.

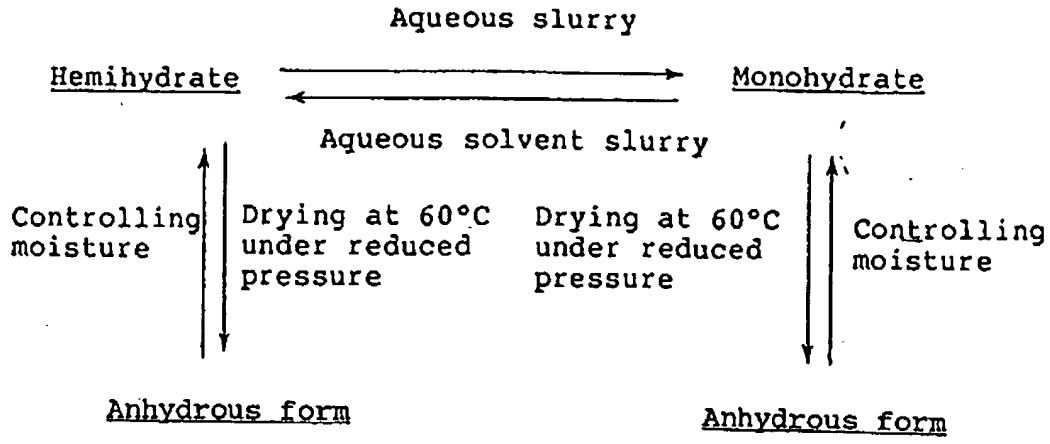
The solvent is preferably used in an amount of about 4 to about 8 times (e.g., about 400 ml to 800 ml/100 g; about 41 to 81/1 kg; and so on), by volume, the amount, on a weight basis, of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido-[1,2,3-de][1,4]benzoxazine-6-carboxylic acid, more preferably 5 to 6 times the amount of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid.

A preferred embodiment of this aspect of the present invention comprises treating (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid by dissolving in an aqueous solvent upon heating. Preferably, the heating temperature ranges from about 50 to about 80°C. More preferable, the heating temperature is about 80°C.

Another embodiment of this aspect of the present invention comprises treating (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid by dissolving in an aqueous solvent upon heating followed by cooling. Preferably, the cooling temperature ranges from about -5 to about 25°C. More preferably, the cooling temperature is about 5°C. The cooling is preferably conducted for about 2 to about 20 hours, more preferably for about 4 hours.

In the method for preparing the monohydrate the solvent has a water content which substantially prevents hemihydrate formation, i.e. more than 10% water. The aqueous solvent is preferably aqueous ethanol.

In addition to the hemihydrate (levofloxacine) and monohydrate crystal forms, (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo- 2,3-dihydro-7H-pyrido-[1,2,3-de][1,4]benzoxazine-6-carboxylic acid crystals may exist as anhydrous crystals. The present inventors examined the conversion of these crystals from one form to another, and thus successfully developed a method for converting hydrated and anhydrous crystals from one crystal form to another. The conversion method is summarized below.



Among the conversion processes shown above, the conversion of the monohydrate into the hemihydrate will be described below.

In order to obtain the hemihydrate from the monohydrate, the monohydrate may be preferably treated by stirring a slurry of the monohydrate in an aqueous solvent with a specific water content of about 2 to about 10%. The conversion rate during this process is affected by the water content and treating temperature. Namely, the conversion rate for obtaining the hemihydrate at a constant temperature increases with decrease of the water content of the aqueous solvent. On the other hand, the conversion rate in an aqueous solvent with a constant water content increases with elevation of the treating temperature. For example, the conversion of the monohydrate into the hemihydrate in aqueous ethanol with a water content of 4% at 25°C completes within about 30 minutes, while requiring about 5 hours at the same water content at 15°C. The conversion in aqueous ethanol with a water content of 8% at 40°C completes within about 30 minutes, while the conversion hardly proceeds at 25°C or below at the same water content.

A slurry can be prepared by mixing crystals with the solvent employed or by precipitating crystals from the solution of crystals.

As described above, the conversion of a hydrate is affected by the water content of the solvent employed, and the temperature and period of the treatment. As described above, a lower water content is preferable, e.g., 10% or less, more preferably 2 to 10%.

Any water miscible solvent may be used in the conversion of the monohydrate into the hemihydrate if the monohydrate is soluble therein. Examples include lower alcohols such as methanol, ethanol and propanol, and acetone. Among these solvents, ethanol is most preferable.

On the other hand, the conversion of the hemihydrate into the monohydrate may be conducted by stirring a slurry of the hemihydrate in water or an aqueous solvent with a specific water content. Similar to the conversion from monohydrate into hemihydrate, the conversion rate from hemihydrate into monohydrate in this instance is affected by various factors including temperature. The conversion in water proceeds more rapidly at a higher temperature. For example, the conversion completes within about 4 hours at 40°C but requires about 42 hours at 5°C.

Contrary to the conversion from the monohydrate to the hemihydrate, a high water content is preferable, e.g., 10% or more.

The stabilities of the hemihydrate and monohydrate in a slurry in an aqueous solvent were examined. As a result, it has been revealed that the stabilities of the hydrates in a slurry in an aqueous solvent depend on the water content of the aqueous solvent employed, the treating temperature and the treating period.

When the stirring is conducted at a high temperature within a short period of time, the stable form of crystal is the hemihydrate even at a high water content. When the stirring temperature is low, on the other hand, the hemihydrate is present as the stable form at a relatively lower water content even a long period of time.

For example, when the stirring is conducted at 50°C for 60 hours, the hemihydrate is present as the stable form at a water content of 16%. When the water content is elevated to 20%, the monohydrate is present as the stable form. When the stirring is conducted at 40°C, the water content, at which the hemihydrate can be present as the stable form, is as low as 10%. It is possible in this case, however, to prolong the stirring period to 8 hours or longer. At this temperature, the monohydrate is present as the stable form at a water content of 14%, however, both the hemihydrate and monohydrate are observed at a water content of 12%. When the stirring is conducted at 20°C for 24 hours, the hemihydrate is present as the stable form at a water content of 8%, while the monohydrate is present as the stable form at

a water content of 12%. Both hydrates are observed together at a water content of 10%. When the stirring is conducted at 5°C for 3 days, the hemihydrate is present as the stable form at a water content of 6% while the monohydrate is present as the stable form at a water content of 8%.

These results clearly show that the target hemihydrate free from any monohydrate can be obtained by using a solvent of a low water content in the recrystallization or crystallization of levofloxacine, and preferably dissolving the crystals by heating within a short period of time and then immediately conducting the crystallization at a low temperature. On the other hand, the above-mentioned examination on the stabilities of the hydrates in a slurry shows that a process for producing the hemihydrate may be changed into a process for producing the monohydrate by, for example, elevating the temperature or prolonging the period of the treatment.

Based on these findings, particular conditions for the recrystallization or crystallization are discussed. Namely, crude levofloxacine crystals are dissolved in an aqueous solvent by heating and then immediately cooled so as to induce crystallization.

The heating temperature at the dissolution may preferably range from about 50 to about 80°C, more preferably about 80°C. The cooling temperature may range from about -5 to about 25°C, preferably about 5°C. The cooling period may range from about 2 to about 20 hours, preferably about 4 hours.

When the water content of the solvent is, for example, as high as 50% at the dissolution of the crystals, it is sufficient to use about three times as much solvent based on the crystals (volume/weight). In this case, however, the obtained hemihydrate crystals can be contaminated with the monohydrate, which suggests that this ratio of solvent to crystals is unsuitable for producing levofloxacine at such high water content. On the other hand, the amount of the solvent required in the crystallization increases with decrease of the water content (e.g., from 50% to about 5%) of the solvent, for example, 5 to 6 times as much as the crystals. In this case, however, the desired hemihydrate can be exclusively obtained and a high yield of 95% is achieved.

The amount of the solvent may range from about 4 to about 8 times, preferably from 5 to 6 times, based on the amount of the crystals (volume/weight). It is not always required to use the solvent in the amount as specified above from the beginning of the treatment. Namely, the levofloxacine may be preliminarily dissolved in a larger amount of the solvent and then the resulting solution may be concentrated so as to control the amount of the solvent.

Also, the particle size of the crystals obtained by the crystallization can be controlled by adjusting the water content of the solvent. In the case of aqueous ethanol, the particle size increases with increase of the water content. The maximum particle size (about 18 μm) is achieved at a water content of about 11%. When the water content further increases, however, the particle size does not increase further but rather decreases.

Most preferably, the crystallization of levofloxacine is conducted with the use of ethanol with a water content of about 5%, in order to obtain levofloxacine crystals with a small particle size.

Furthermore, it is also possible to employ some purification steps (for example, decoloration with the use of active carbon) between the dissolution of the crude crystals and the recrystallization or crystallization.

Also, in the process of the selective production of an (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate or monohydrate in accordance with the present invention, the water content may be controlled by adding water after mixing (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid with a solvent.

A method for drying the crystals is described below.

The result of differential thermal analysis indicates that crystal water is liberated from crystals of levofloxacine at about 70°C under atmospheric pressure or at about 60°C under reduced pressure to result in anhydrous crystals. The process which comprises completely removing the solvent and the crystal water and then producing the hemihydrate by controlling the moisture is unsuitable, since the anhydride shows a poor property. In order to remove the solvent alone from the aimed product, therefore, the temperature, degree of the reduction of pressure and time of drying must be controlled.

Therefore, the drying temperature preferably ranges from about 20 to about 45°C, more preferably from 35 to 40°C. The reduced pressure preferably ranges from about 6.49×10^{-6}Pa to about 1.30×10^{-6}Pa (about 5 to about 100 mmHg), more preferably from 6.49×10^{-6}Pa to 1.30×10^{-7}Pa (5 to 10 mmHg). The drying time is preferably 8 hours or less.

The drying method is applicable to various dryers, for example, conical-screw drier, vibro-fluidizing drier, double-cone rotating drier or compartment tray drier.

To further illustrate the present invention, and not by way of limitation, the following Examples are given.

EXAMPLE 1

28.9 kg of crude crystals of levofloxacine [(S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate] were dissolved in 375 ℓ of 4% aqueous ethanol under stirring. After adding 0.87 kg of active carbon, the obtained mixture was filtered. The active carbon was washed with 4% aqueous ethanol. The filtrate and the washing liquid were combined and concentrated so as to give a total volume

of about 5 times (volume/ weight) the initial levofloxacine crystals. After the completion of the concentration, the mixture was allowed to cool under stirring overnight. Then, it was allowed to stand while cooling to 7 to 15°C for 3 to 4 hours to thereby induce crystallization. The crystals thus precipitated were collected by filtering. Thus 26.7 kg of the crystals were obtained. These crystals were packed into a conical-screw drier and dried therein under reduced pressure at an elevated temperature for 4 hours. Thus 25.8 kg of dry levofloxacine was obtained. This product was identified as levofloxacine by instrumental analyses. The physical data of the levofloxacine (hemihydrate) are as follows:
Melting point: 223 - 225°C (decomp.)

Elemental analysis: as $C_{18}H_{20}FNO_3O_4 \cdot 1/2H_2O$			
Calculated:	C 58.37,	H 5.71,	N 11.35
Found:	C 58.32,	H 5.43,	N 11.37

Water content (Karl-Fischer's method):	
Calculated:	2.43%
Found:	2.50%

Differential thermal analysis:	
Crystal water liberation point:	72.4°C
Weight change:	2.5% (calculated: 2.43%)
Melting point:	234.0°C

Powder method of X-ray diffraction (characteristic Peak):
$2\theta = 6.7°$
13.2°
IR (characteristic peak): 3440 cm^{-1}
In the above-mentioned analyses, the following instruments were employed.

Water content: MKA-210, Kyoto Denshi Kogyo K.K.
Melting Point: 535, Büch Co. (determined in accordance with The Pharmacopoea of Japan)
Differential thermal analysis: TG/DTA20, Seiko I & E. Controller, SSC/580
Powder method of X-ray diffraction: Geigerflex, Rigaku Denki K.K.
IR: 260-30, Hitachi Electric Co.

EXAMPLE 2

5.05 kg of crude levofloxacine crystals and 5% aqueous ethanol were treated in the same manner as described in Example 1 resulting in 5.0 kg of crystals. These crystals were packed into a vibro-fluidizing drier and dried under reduced pressure for about 3.5 hours. Thus 4.67 kg of dry levofloxacine was obtained.

EXAMPLE 3

13.2 kg of crude levofloxacine crystals and 5% aqueous ethanol were treated in the same manner as the one described in Example 1 resulting in 5.0 kg of crystals. These crystals were packed into a double-cone rotating drier and dried for about 3.5 hours. Thus 12.1 kg of dry levofloxacine was obtained.

EXAMPLE 4

5 g of crude levofloxacine crystals were added to 25 ml of water and formulated into a slurry. The obtained slurry was stirred at 25°C for 20 hours. The crystals were collected by filtering, washed with 5 ml of water and dried at room temperature under reduced pressure. When a constant weight was achieved, 4.76 g of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylic acid monohydrate was obtained. The analysis on these crystals by the powdery method of X-ray diffraction proved that the product was the monohydrate.

The physical date of the monohydrate are as follows:
Melting point: 225 - 228°C (decomp.)

Elemental analysis: as $C_{18}H_{20}FNO_3O_4 \cdot H_2O$			
Calculated:	C 56.93,	H 5.80,	N 11.07
Found:	C 57.05,	H 6.11,	N 11.05

Water content (Karl-Fischer's method):	
Calculated:	4.74%
Found:	4.70%

Differential thermal analysis:	
Crystal water liberation point:	62.0°C
Weight change:	4.8% (calculated: 4.74%)
Melting point:	232.7°C

Powder method of X-ray diffraction (characteristic peak):
2θ = 8.0°
11.5°
16.7°
18.0°
22.5°
IR (characteristic peak): 3540, 3440 cm^{-1}
In the above-mentioned analyses, the same instruments as described in Example 1 were employed.

EXAMPLE 5

5 g of crude levofloxacine crystals were added to 50 ml of water and then treated in the same manner as described in Example 4. Thus 4.44 g of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[l,2,3-de][1,4]-benzoxazine-6-carboxylic acid monohydrate was obtained.

The process of the present invention enables the selective production of levofloxacine, i.e., crystalline hemihydrate, from (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]-benzoxazine-6-carboxylic acid, which occurs in several crystalline forms, on an industrial scale. In addition, it enables the production of the monohydrate. Furthermore, it enables the adjustment of the particle size of the target compound by controlling the crystallization conditions. Thus, crystals of an appropriate particle size can easily be obtained. In addition, the drying method in accordance with the present invention is applicable to various drying systems.

Therefore the process of the present invention is highly useful from industrial and economical viewpoints.

Claims

1. A process for selectively producing (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate, which comprises

   (i) stirring a slurry of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperainyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid monohydrate or a mixture of the monohydrate and the hemihydrate thereof in an aqueous water miscible solvent containg water in an amount of 10 % by volume or less, at a temperature and for a period of time appropriate to substantially avoid monohydrate formation,

   (ii) dissolving crude levofloxacine or said monohydrate or a mixture of said monohydrate and said hemihydrate in an aqueous water miscible solvent which is selected from methanol, ethanol, propanol and acetone and which contains 2 to 10 % water by volume, under conditions which substantially avoid monohydrate formation, the solvent being used in an amount, by volume, of 4 to 8 times the amount, on a weight basis, of said mono-

hydrate or said mixture, and crystallizing the hemihydrate from said solvent by cooling or

(iii) dissolving anhydrous (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido [1,2,3-de][1,4]benzoxazine-6-carboxylic acid in an aqueous solvent which is selected from methanol, ethanol, propanol and acetone and which contains 2 to 10 % water by volume, under conditions which substantially avoid monohydrate formation, the solvent being used in an amount, by volume, of 4 to 8 times the amount, on a weight basis, of said anhydrous carboxylic acid, and crystallizing the hemihydrate from said solvent by cooling.

2. The process as claimed in Claim 1, wherein in methods (i), (ii), or (iii) said solvent is aqueous ethanol.

3. The process as claimed in Claim 1 or 2, wherein the water content of said solvent ranges from 4 to 5 %.

4. The process as claimed in any one of the preceding claims, wherein said solvent is used in an amount, by volume, of 5 to 6 times the amount, on a weight basis, of said anhydrous (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid or the monohydrate thereof or said mixture.

5. The process as claimed in any one of the preceding claims, wherein said anhydrous (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid or the monohydrate thereof or said mixture is dissolved in said solvent under heating.

6. The process as claimed in Claim 5, wherein the heating temperature ranges from 50 to 80°C.

7. The process as claimed in Claim 6, wherein the heating temperature is 80°C.

8. The process as claimed in any one of the preceding claims, wherein the cooling temperature ranges from -5 to 25°C.

9. The process as claimed in Claim 8, wherein the cooling temperature is 5°C.

10. The process as claimed in any one of the preceding claims wherein said cooling is conducted for 2 to 20 hours.

11. The process as claimed in Claim 10, wherein said cooling is conducted for 4 hours.

12. The process as claimed in any one of the preceding claims, further comprising removing said solvent from the hemihydrate crystals formed by applying a drying temperature ranging from 20 to 45°C, a reduced pressure ranging from 6.49×10^{-8} Pa to 1.30×10^{-6} Pa (5 to 100 mmHg), and a drying time of 8 hours or less.

13. The process as claimed in any one of the preceding claims, wherein in methods ii) and iii) crude levofloxacin is dissolved in said aqueous solvent.

14. A process for selectively producing (S)-9-fluoro-3-methyl-10-1(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-7-carboxylic acid monohydrate which comprises stirring a slurry of (S)-9-fluoro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylic acid hemihydrate or a mixture of the hemihydrate and the monohydrate thereof in water or an aqueous solvent containing more than 10 % water at a temperature and for a period of time apropriate to substantially avoid hemihydrate formation.

15. The process as claimed in Claim 14, wherein the aqueous solvent is water.

16. The process as claimed in Claim 15, wherein said aqueous solvent is aqueous ethanol.

Patentansprüche

1. Verfahren zur selektiven Herstellung von (S)-9-Fluor-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäurehemihydrat, umfassend:

(i) das Rühren einer Aufschlämmung von (S)-9-Fluor-3-methyl-10-(4-methyl-I-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäuremonohydrat oder eines Gemisches des Monohydrates und des Hemihydrates davon in einem wäßrigen, mit Wasser mischbaren Lösungsmittel, welches Wasser in einer Menge von 10 Vol.-% oder weniger enthält, bei einer Temperatur und Dauer, bei denen eine Monohydratbildung im wesentlichen vermieden werden kann,
(ii) das Lösen rohen Levofloxacins oder des Monohydrats oder eines Gemisches des Monohydrates mit dem Hemihydrat in einem wäßrigen, mit Wasser mischbaren Lösungsmittel, das ausgewählt ist unter Methanol, Ethanol, Propanol und Aceton und das 2 bis 10 Vol.-% Wasser enthält, unter Bedingungen, bei denen eine Monohydratbildung im wesentlichen vermieden wird, wobei das Lösungsmittel in einer auf das Volumen bezogenen Menge verwendet wird, die der 4- bis 8- fachen Gewichtsmenge des Monohydrates oder des Gemisches entspricht, und Kristallisieren des Hemihydrates aus dem Lösungsmittel durch Abkühlen, oder
(iii) Lösen von wasserfreier (S) -9-Fluor-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido [1,2,3-de][1,4]benzoxazin-6-carbonsäure in einem wäßrigen Lösungsmittel, das ausgewählt ist unter Methanol, Ethanol, Propanol und Aceton und das 2 bis 10 Vol.-% Wasser enthält, unter Bedingungen, bei denen eine Monohydratbildung im wesentlichen vermieden wird, wobei das Lösungsmittel in einer auf das Volumen bezogenen Menge verwendet wird, die der 4- bis 8-fachen Gewichtsmenge des Monohydrates oder des Gemisches entspricht, und Kristallisieren des Hemihydrates aus dem Lösungsmittel durch Abkühlen.

2. Verfahren nach Anspruch 1, wobei das Lösungsmittel in den Methoden (i), (ii) oder (iii) wäßriges Ethanol ist.

3. Verfahren nach Anspruch 1 oder 2, wobei der Wassergehalt des Lösungsmittels im Bereich von 4 bis 5 % liegt.

4. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Lösungsmittel in einer auf das Volumen bezogenen Menge verwendet wird, die der 5- bis 8-fachen Gewichtsmenge der wasserfreien (S)-9-Fluor-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäure oder des Monohydrates davon oder des Gemisches entspricht.

5. Verfahren nach einem der vorhergehenden Ansprüche, wobei die wasserfreie (S)-9-Fluor-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäure oder das Monohydrat davon oder das Gemisch unter Erwärmen in dem Lösungsmittel gelöst wird.

6. Verfahren nach Anspruch 5, wobei die Erwärmungstemperatur im Bereich von 50 bis 80°C liegt.

7. Verfahren nach Anspruch 6, wobei die Erwärmungstemperatur 80°C beträgt.

8. Verfahren nach einem der vorhergehenden Ansprüche, wobei die Abkühlungstemperatur im Bereich von -5 bis 25°C liegt.

9. Verfahren nach Anspruch 8, wobei die Abkühlungstemperatur 5°C beträgt.

10. Verfahren nach einem der vorhergehenden Ansprüche, wobei 2 bis 20 Stunden abgekühlt wird.

11. Verfahren nach Anspruch 10, wobei 4 Stunden abgekühlt wird.

12. Verfahren nach einem der vorhergehenden Ansprüche, wobei zusätzlich das Lösungsmittel aus den gebildeten Hemihydratkristallen durch Anwendung einer Trocknungstemperatur im Bereich von 20 bis 45°C, eines reduzierten Drucks im Bereich von $6{,}49 \times 10^{-8}$ Pa bis $1{,}30 \times 10^{-6}$ Pa (5 bis 100 mmHg) und einer Trocknungszeit von 8 Stunden oder weniger entfernt wird.

13. Verfahren nach einem der vorhergehenden Ansprüche, wobei in dem wäßrigen Lösungsmittel bei den Methoden ii) und iii) rohes Levofloxacin gelöst wird.

14. Verfahren zur selektiven Herstellung von (S)-9-Fluor-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäuremonohydrat, umfassend das Rühren einer Aufschlämmung von (S)-9-Fluor-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazin-6-carbonsäurehemihydrat oder eines Gemischs des Monohydrates und des Hemihydrates davon in Wasser oder einem wäßrigen, mit Wasser mischbaren Lösungsmittel, welches mehr als 10 % Wasser enthält, bei einer Temperatur und Dauer, bei denen eine Hemihydratbildung im wesentlichen vermieden werden kann.

15. Verfahren nach Anspruch 14, wobei das wäßrige Lösungsmittel Wasser ist.

16. Verfahren nach Anspruch 15, wobei das wäßrige Lösungsmittel wäßriges Ethanol ist.

Revendications

1. Procédé de production sélective de l'acide (S)-9-fluoro-3-méthyl-10-(4-méthyl-1-pipérazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique hémihydraté, qui comprend

   (i) agiter une pâte d'acide (S)-9-fluoro-3-méthyl-10-(4-méthyl-1-pipérazinyl)-7oxo-2,3-dihydro-7H-pyrido [1,2,3-de][1,4]benzoxazine-6-carboxylique monohydraté ou un mélange de monohydrate et de son hémihydrate dans un solvant aqueux miscible à l'eau contenant de l'eau en une quantité de 10% en volume ou moins, à une température et pendant une période appropriée pour éviter sensiblement la formation de monohydrate,
   (ii) dissoudre ladite lévofloxacine monohydrate ou un mélange dudit monohydrate et dudit hémihydrate dans un solvant aqueux miscible à l'eau qui est choisi parmi le méthanol, l'éthanol, le propanol et l'acétone et qui contient 2 à 10% d'eau en volume, dans des conditions qui évitent sensiblement la formation du monohydrate, le solvant étant utilisé en une quantité, en volume, de 4 à 8 fois la quantité, sur une base pondérale, dudit monohydrate ou dudit mélange, et cristalliser l'hémihydrate à partir dudit solvant en refroidissant, ou
   (iii) dissoudre l'acide (S)-9-fluoro-3-méthyl-10-(4-méthyl-1-pipérazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de] [1,4]benzoxazine-6-carboxylique anhydre dans un solvant aqueux qui est choisi parmi le méthanol, l'éthanol, le propanol et l'acétone et qui contient 2 à 10% d'eau en volume, dans des conditions qui évitent sensiblement la formation de monohydrate, le solvant étant utilisé en une quantité, en volume, de 4 à 8 fois la quantité, sur une base pondérale, dudit acide carboxylique anhydre, et
   cristalliser l'hémihydrate à partir du solvant par refroidissement.

2. Procédé selon la revendication 1, où dans les procédés (i), (ii) ou (iii) ledit solvant est de l'éthanol aqueux.

3. Procédé selon la revendication 1 ou 2, où la teneur en eau dudit solvant est comprise entre 4 et 5%.

4. Procédé selon l'une quelconque des revendications précédentes, où ledit solvant est utilisé en une quantité, en volume, de 5 à 6 fois la quantité, sur une base pondérale, dudit acide (S)-9-fluoro-3-méthyl-10-(4-méthyl-1-pipérazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique anhydre ou son monohydrate ou ledit mélange.

5. Procédé selon l'une quelconque des revendications précédentes, où ledit acide (S)-9-fluoro-3-méthyl-10-(4-méthyl-1-pipérazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique ou son monohydrate ou ledit mélange est dissous dans ledit solvant en chauffant.

6. Procédé selon la revendication 5, où la température de chauffage est comprise entre 50 et 80°C.

7. Procédé selon la revendication 6, où la température de chauffage est 80°C.

8. Procédé selon l'une quelconque des revendications précédentes, où la température de chauffage est comprise entre -5 et 25°C.

9. Procédé selon la revendication 8, où la température de refroidissement est 5°C.

10. Procédé selon l'une quelconque des revendications précédentes, où ledit refroidissement est réalisé pendant 2 à 20 h.

11. Procédé selon la revendication 10, où on réalise ledit refroidissement pendant 4 h.

12. Procédé selon l'une quelconque des revendications précédentes, qui comprend en outre d'éliminer ledit solvant des cristaux hémihydrate formés en appliquant une température de séchage comprise entre 20 et 45°C, une pression réduite comprise entre $6,49 \times 10^{-8}$ Pa et $1,30 \times 10^{-6}$ Pa (5 à 100 mmHg), et une durée de séchage de 8 h ou moins.

13. Procédé selon l'une quelconque des revendications précédentes, où dans les procédés (ii) et (iii) on dissout la lévofloxacine dans ledit solvant aqueux.

14. Procédé de production sélective de l'acide (S)-9-fluoro-3-méthyl-10-(4-méthyl-1-pipérazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique monohydrate qui comprend d'agiter une pâte d'acide (S)-9-fluoro-3-méthyl-10-(4-méthyl-1-pipérazinyl)-7-oxo-2,3-dihydro-7H-pyrido[1,2,3-de][1,4]benzoxazine-6-carboxylique hémihydrate ou un mélange d'hémihydrate et de son monohydrate dans l'eau ou un solvant aqueux contenant plus de 10% d'eau à une température et pendant une période de temps appropriée pour éviter sensiblement la formation d'hémihydrate.

15. Procédé selon la revendication 14, où le solvant aqueux est de l'eau.

16. Procédé selon la revendication 15, où ledit solvant aqueux est de l'éthanol aqueux.